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Genetic Cancer Risk Assessment and Counseling: Recommendations of the National Society of Genetic Counselors

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These cancer genetic counseling recommendations describe the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through

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cancer risk assessment with or without genetic testing. They were developed by members of the Practice Issues Subcommittee of the National Society of Genetic Counselors Cancer Genetic Counseling Special Interest Group. The information contained in this document is derived from extensive review of the current literature on cancer genetic risk assessment and counseling as well as the personal expertise of genetic counselors specializing in cancer genetics. The recommendations are intended to provide information about the process of genetic counseling and risk assessment for hereditary cancer disorders rather than specific information about individual syndromes. Key components include the intake (medical and family histories), psychosocial assessment (assessment of risk perception), cancer risk assessment (determination and communication of risk), molecular testing for hereditary cancer syndromes (regulations, informed consent, and counseling process), and follow-up considerations. These recommendations should not be construed as dictating an exclusive course of management, nor does use of such recommendations guarantee a particular outcome. These recommendations do not displace a health care provider's professional judgment based on the clinical circumstances of a client.

KEY WORDS: cancer genetic counseling; risk assessment; genetic testing; family history; psychosocial assessment.

PURPOSE

The purpose of this document is to present a set of practice recommendations for genetic counselors conveying cancer genetic risk counseling. These recommendations will describe the complexity of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without genetic testing. The guidelines are intended to provide background information about the process of genetic counseling and risk assessment for hereditary cancer rather than to provide information about specific hereditary cancer syndromes. The guideline was developed by cancer genetic counselors who are members of the Practice Issues Subcommittee of the National Society of Genetic Counselor's (NSGC) Cancer Genetic Counseling Special Interest Group. This guideline has been reviewed by additional cancer genetic counselors, members of the American College of Medical Genetics (ACMG) and the Oncology Nursing Society, consumer groups, NSGC general membership, and the Board of Directors and Genetic Services Committee of the NSGC. The information contained in this document was derived from an extensive review of the current literature on cancer genetic risk assessment and counseling as well as the personal expertise of genetic counselors specializing in cancer genetics.

DISCLAIMER

The genetic counseling recommendations of the NSGC are developed by members of the NSGC to assist practitioners and patients in making decisions

about appropriate management of genetic concerns. Each practice recommendation focuses on a clinical or practice issue and is based on a review and analysis of the professional literature. The information and recommendations reflect scientific and clinical knowledge current as of the submission date and are subject to change as advances in diagnostic techniques, treatments, and psychosocial understanding emerge. In addition, variations in practice, taking into account the needs of the individual patient and the resources and limitations unique to the institution or type of practice, may warrant approaches, treatments, or procedures alternative to the recommendations outlined in this document. Therefore, these recommendations should not be construed as dictating an exclusive course of management, nor does use of such recommendations guarantee a particular outcome. Genetic counseling recommendations are never intended to displace a health care provider's best medical judgment based on the clinical circumstances of a particular patient.

METHODOLOGY

The authors consisted of a subcommittee of the Practice Issues Subcommittee of the NSGC Cancer Genetic Counseling Special Interest Group. The authors searched via MEDLINE the relevant English language medical and psychosocial literature between 1989 and 2002, with several key seminal articles from earlier dates. Key words included cancer genetics, genetic counseling, psychosocial assessment, and gene testing. Published guidelines and policy statements published by American Society of Clinical Oncology (ASCO, 1996, 2003), ACMG Foundation (1999), American Society of Human Genetics (ASHG, 1994), National Action Plan on Breast Cancer (NAPBC, 1998), and cancer genetic counseling guidelines developed by genetic counselors in the state of Washington (adaptation of Marymee et al., 1998), and the Task Force on Genetic Testing (NIH-DOE/ELSI Task Force, 1997) were also reviewed. This literature is based on clinical experience, descriptive studies, and/or reports of expert committees. The literature was reviewed and evaluated for quality according to the categories outlined by the U.S. Preventive Services Task Force (1995):

I. Evidence obtained from at least one properly designed randomized controlled trial
   II-1. Evidence obtained from well-designed controlled trials without randomization
   II-2. Evidence obtained from well-designed cohort or case-control-analytic studies, preferably from more than one center or research group
   II-3. Evidence obtained from multiple time series with or without the intervention
III. Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

The rating of supporting literature for this recommendation is III.

A draft document was made available to the 2,072 members of NSGC for comment in October 2003. The NSGC membership includes genetic counselors, physicians, nurses, attorneys, doctors of philosophy, and students. The revised document was reviewed by the NSGC attorney and the NSGC Ethics Subcommittee and no conflicts with the NSGC Code of Ethics or issues regarding legal liability were identified in the final document. All 20 members of the NSGC Board of Directors reviewed and unanimously approved the final document in November 2003.

INTRODUCTION

All cancers develop because of an accumulation of mutations in genes that, when functioning normally, promote regulated cell growth and DNA integrity (Fearon and Vogelstein, 1990; Vogelstein and Kinzler, 1993). Mutations in tumor suppressor genes, including DNA repair genes, and proto-oncogenes have been implicated in carcinogenesis (Table I). In most cases, mutations in these genes are acquired by chance or as the result of environmental exposures (Amos, 1994; Chen *et al.*, 1994; Willett, 1993), so-called somatic mutations. Approximately one in two males and one in three females in the United States will develop cancer in their lifetime (American Cancer Society, 2002). Most of these cancers are attributable to age-related risk factors that result from a lifetime of environmental exposures and/or chance DNA replication errors that lead to mutations in tumor suppressors and proto-oncogenes. Subsets are due, in part, to known carcinogens, a comprehensive list of which is available through the U.S. Department of Health and Human Services Environmental Health Information Service's Report on Carcinogens (http://ehp/niehs.nih.gov/roc/ or http://ehis.niehs.nih.gov/). Members of some families are prone to developing specific types of malignancies in the absence of an identifiable carcinogenic exposure. Affected individuals in these families may represent clustering of sporadic occurrences, multifactorial inheritance, or the presence of a low penetrance gene(s). These groupings are classified as familial cancers. Close relatives are at moderately increased risk of developing certain malignancies. However, the average age of onset is usually similar to that observed in the general population. In contrast, in about 5–10% of individuals with cancer occurrences, predisposition to a specific group of cancers is the result of a heritable mutation in a cancer predisposition gene, that is, a germline mutation. At-risk individuals tend to develop benign and/or malignant tumors at an earlier age than usual and are at increased risk of developing more than one primary tumor. In addition, the siblings and offspring of an affected person each have a 50% chance of inheriting the cancer-predisposing mutation segregating in the family, consistent with autosomal dominant inheritance, in most cases.

Table I. Selected Hereditary Syndromes Associated With an Increased Risk of Common Cancers

Syndrome	Associated malignancies/features	Causative gene(s)
Hereditary breast cancer; hereditary breast/ovarian cancer; OMIM numbers: 113705, 600185, 114480	Breast cancer in females and males, ovarian and prostate cancers and other cancers, depending on the gene in question	*BRCA1*, *BRCA2*, probably other gene(s)
Hereditary nonpolyposis colorectal cancer (HNPCC); OMIM numbers: 114500, 120435, 120436, 600259, 600258, 158320, 600678, 276300	Early-onset colorectal cancer, endometrium, ovary, small bowel, stomach, pancreas, ureter, and renal pelvis *Muir–Torre syndrome* is HNPCC with sebaceous adenomas, sebaceous adenocarcinomas, and keratoacanthomas. HNPCC plus glioma or glioblastoma multiforme is designated as *Turcot syndrome*	DNA mismatch repair genes—*MLH1*, *MSH2*, *PMS1*, *PMS2*, *MSH6*, *MSH3*
Cowden syndrome; OMIM number: 158350, 601299	Breast cancer, thyroid cancer, endometrial cancer, and benign hamartomatous lesions of the skin, oral mucosa and intestine and benign breast and thyroid disease	*PTEN* (Eng, 2000)
Familial adenomatous polyposis (FAP); Attenuated FAP; OMIM numbers: 175100, 276300	Adenomatous polyposis, colorectal cancer, papillary thyroid cancer, gastric cancer, periampullary carcinoma, adrenal cancer, hepatoblastoma and extracolonic manifestations. Polyposis with extracolonic features was formerly designated as *Gardner syndrome*. Polyposis with brain tumors, predominantly medulloblastoma, is designated as *Turcot syndrome*. less than 100 colonic polyps, predominance of right-sided polyps, later-onset colorectal cancer (>40). May be increased risk of gastric and duodenal adenomas and/or cancer	*APC*
Juvenile polyposis syndrome; OMIM number: 174900, 601299	Hamartomatous polyps, increased risk for colorectal, pancreatic, gastric and duodenal cancer	*MADH4* (Howe *et al.*, 1998); *BMPR1A/ALK3* (Eng, 2001; Howe *et al.*, 2001; Zhou *et al.*, 2001)
Hereditary prostate cancer; OMIM numbers: 176807, 601518, 300147, 605367, 602759, 603688	Prostate cancer and possible increased risk of other cancers depending on the implicated gene	*HPC1/RNASEL*, (Carpten *et al.*, 2002), *HPC2/ELAC2* (Tavtigian *et al.*, 2001), *MSR1* (Xu *et al.*, in press)
Basal cell nevus syndrome; (Gorlin syndrome); OMIM number: 109400	Basal cell nevi, characteristics facies, palmar and plantar pits, odontogenic keratocysts, rib abnormalities, increased risk of basal cell carcinoma, ovarian carcinoma, ovarian fibromata	*PTCH*

Table I. (*Continued*)

Syndrome	Associated malignancies/features	Causative gene(s)
Familial atypical mole malignant melanoma syndrome/hereditary dysplastic nevus syndrome; OMIM number: 155600, 123829, 155601, 600160	Multiple primary melanomas, dysplastic nevi, pancreatic cancer	*CDKN2A* ($p16^{INK4a}/p14^{ARF}$), *CDK4*

Note. Adapted from Online Mendelian Inheritance in Man, OMIM (TM). Center for Medical Genetics, Johns Hopkins University (Baltimore, MD), and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), 2002. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/

[a] Variable expressivity within and among families. Some patients may have few of the associated findings whereas others may have most of them.

Hereditary syndromes predisposing individuals to common malignancies such as breast, ovarian, colon, prostate, melanoma, and endometrial cancer have been described (Table I; Offit, 1998). In addition, a number of syndromes predisposing to rare cancers have been recognized (Table II). In all these conditions, cancer risks in mutation carriers vary depending on the syndrome, the specific mutation in the family, and sometimes gender. However, cancer risks can approach 85–100% over a lifetime. Hereditary cancers tend to develop at a younger age than expected, often prior to the time at which general population screening would be initiated. Furthermore, many syndromes predispose to cancers for which screening is not routinely performed. Therefore, identification of individuals at increased risk of cancer may have implications for both screening and clinical management.

Cancer genetic risk assessment and genetic counseling is the process of identifying and counseling individuals at risk for familial or hereditary cancer. Cancer genetic risk assessment involves use of pedigree analysis with available risk assessment models to determine whether a family history is suggestive of sporadic, familial, or hereditary cancer. The purpose of classifying the family history is to help quantify cancer risks in individuals and their biological relatives, and to facilitate syndrome identification. This information is useful in developing a plan of management for cancer screening, prevention, and risk reduction, and in understanding the psychological and emotional responses that occur for those at increased risk of developing cancer. In addition, classification aids in determining if molecular testing is available and whether testing will further characterize cancer risks in a family (Schneider and Garber, 2001).

Genetic counseling is an integral part of the cancer risk assessment process (Peters and Stopfer, 1996). The purpose of cancer genetic counseling is to educate clients about their chance of developing cancer, help them derive personal meaning from cancer genetic information, and empower them to make educated, informed decisions about genetic testing, cancer screening, and cancer prevention. Informed

Table II. Selected Rare Hereditary Cancer Syndromes

Syndrome	Associated malignancies/clinical features	Genes implicated
Li–Fraumeni syndrome; OMIM number: 151623, 191170	Breast cancer, soft tissue sarcomas, osteosarcomas, adrenocortical carcinoma, leukemia, brain tumors	*TP53*, *CHEK2*
Peutz–Jeghers syndrome; OMIM number: 175200, 602216	Breast cancer, benign ovarian tumors, testicular tumors, pancreatic cancer, polyps of the ureter, bladder, GI tract (hamartomatous polyps), renal pelvis, bronchus, nasal passage. Melanin spots on lips, buccal mucosa, and digits	*STK11/LKB1*
Hereditary retinoblastoma; OMIM number: 180200	Retinoblastomas, often bilateral or multifocal, other malignancies like osteosarcomas, especially in response to radiation exposure	*RB1*
von Hippel–Lindau syndrome; OMIM number: 193300	Hemangioblastomas of the brain, spine, and retina, pheochromocytoma, renal cell carcinoma, epididymal cystadenoma, endolymphatic sac tumors	*VHL*
Multiple endocrine neoplasia type I; OMIM number: 131100	Zollinger-Ellison syndrome. Parathyroid tumors, hyperparathyroidism, pituitary tumors, pancreatic islet tumors	*MEN1*
Multiple endocrine neoplasia type II (include familial medullary thyroid cancer [FMTC]); OMIM number: 171400, 164761	MEN2A: Medullary thyroid carcinoma (MTC), pheochromocytoma, parathyroid tumors/parathyroid hyperplasia (PTH). MEN2B: Associated with and earlier onset of MTC and pheochromocytomas as well as mucosal neuromas and a Marfanoid habitus	*RET*
Pheochromocytoma; OMIM number: 171300, 602690, 193300, 164761, 185470	Adrenal medullary tumors, isolated pheochromocytomas and/or paragangliomas	*RET*, *VHL*, *SDHD*, *SDHB* (Neumann *et al.*, 2002)
Nonchromaffin paraganglioma; OMIM number: 168000, 602690, 605373, 601650	Paragangliomas, chemodectomas, carotid body tumors, glomus jugular tumors, pheochromocytoma	*PGL1/SDHD PGL2* (11q13.1) (maternal imprinting for above two genes) *PGL3/SDHC* (no imprinting) (Drovdlic *et al.*, 2001)
Wilms tumor; OMIM number: 194070, 194071, 194090, 601583, 601363, 607102	Nephroblastoma; can also be associated with WAGR, Beckwith–Wiedemann and other abnormal urogenital development syndromes	*WT1* (Other putative loci)

Note. Adapted from Online Mendelian Inheritance in Man, OMIM (TM). Center for Medical Genetics, Johns Hopkins University (Baltimore, MD), and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD), 2002. World Wide Web URL: http://www.ncbi.nlm.nih.gov/omim/

decision-making requires understanding and integrating genetic, medical, and psychosocial information (Geller *et al.*, 1997). Although education is an important part of the decision-making process, attention to psychosocial issues is critical for cancer genetic risk assessment and genetic counseling to be effective (Lerman *et al.*, 1995, 1997). As a result, psychosocial assessment is a key component of the genetic counseling process.

A referral for cancer genetic risk assessment and counseling should be considered for clients with personal or family history features suggestive of familial or hereditary cancer and should not be limited to just those individuals who are potential candidates for genetic testing. Individuals from high-risk families may benefit from a detailed discussion about the heritability of cancer in their families, appropriate cancer risk management strategies, and the option of genetic testing.

This document has been prepared to help health care providers identify clients who may benefit from cancer risk assessment and genetic counseling and to understand the components of the process. Because of the number of issues involved, comprehensive cancer genetic risk assessment and counseling benefits from a multidisciplinary approach. Access to board-certified or board-eligible genetic counselors, medical geneticists, surgeons, oncologists, social workers, oncology nurses, psychologists, and other relevant professionals can help the client address different informational, medical, and psychosocial needs.

THE CANCER GENETIC RISK ASSESSMENT AND COUNSELING PROCESS

Intake

The first step of cancer risk assessment and counseling begins with collection of a client's personal and family medical history. Intake information can be obtained via a questionnaire completed prior to a cancer risk consultation or during the consultation. Collecting information prior to the consult allows the clinician to obtain confirmatory medical records and assess the significance of the family history in advance of the session.

Personal Medical History

Table III lists the information to be collected while obtaining the client's medical history for individuals with and without a previous cancer diagnosis. Information to be obtained includes the frequency of cancer surveillance, the date and results of recent screening examinations and details about pertinent environmental exposures such as occupation, alcohol consumption**,** tobacco use, and diet (Bennett, 1999; Schneider and Garber, 2001).

Table III. Collecting a Personal Medical History: Questions to Ask Patients With and Without Cancer

Questions to ask all patients	Questions to ask patients who have had cancer/or regarding relatives with cancer
• Age	• Organ in which tumor developed
• Personal history of benign or malignant tumors	• Age at time of diagnosis
• Major illnesses	• Number of tumors[a]
• Hospitalizations	• Pathology, stage, and grade of malignant tumor
• Surgeries	• Pathology of benign tumors
• Biopsy history	• Treatment regimen (surgery, chemotherapy, radiation)
• Reproductive history[b]	
• Cancer surveillance	
• Environmental exposures	

[a] For patients who have developed more than one tumor, it is important to discriminate whether the additional tumor(s) was a separate primary, recurrence, or the result of metastatic disease.

[b] Especially important for women at increased risk of breast, ovarian, or endometrial cancer. Inquire about age at menarche, age at first live birth, and history of oral contraceptive use, infertility medications, or hormone replacement therapy including dosage and duration, age at menopause.

Family History

Procuring and analyzing a genetic pedigree is the cornerstone of cancer genetic risk assessment (Bennett, 1999). There is a chance of underascertainment of high-risk families unless an accurate, comprehensive family history is obtained from both new and returning patients (Sweet *et al.*, 2002). At minimum, a three- to four-generation pedigree, including detailed medical information about the proband's first-, second-, and, ideally, third-degree relatives should be obtained. Standardized pedigree nomenclature should be used (Bennett *et al.*, 1995). Gathering information about both paternal and maternal family history, ancestry/ethnicity, and consanguinity is necessary. For relatives who have had a cancer diagnosis, document health and carcinogen exposure information (see Table III). For relatives who are deceased, note the cause of death and age.

Erroneous cancer family history reporting has been documented in the medical literature (Love *et al.*, 1985; Theis *et al.*, 1994) and can affect medical management and risk assessment (Douglas *et al.*, 1999). Accurate family risk assessment requires medical record confirmation of key cancer diagnoses. Whenever possible, obtain confirmation of relevant cancer diagnoses in the family prior to genetic testing. In the absence of medical record confirmation, inform the client that the assessment of his/her heritable cancer risk can change substantially should records later reveal fewer, greater, or different cancer diagnoses than reported. Also, because cancer genetic risk assessment is a dynamic process, a person's estimated cancer risk can change if additional relatives are diagnosed with cancer. Therefore, encourage individuals undergoing cancer genetic risk assessment to report any changes in their family history.

Document on the pedigree and/or in the clinical summary any pertinent information obtained through medical record review. Record information from relatives' medical records in a manner that attempts to maintain confidentiality.

Psychosocial Assessment

An individual's decision to seek and utilize information regarding cancer genetics is based on a variety of factors. Assessment of psychosocial issues is the optimal method for the clinician to appreciate all of the factors that affect risk perception and ultimately, utilization of cancer genetic information (Biesecker, 1997; Croyle, 1997; Hopwood, 1997; Lerman and Croyle, 1996). This process can also enlighten the provider on the potential impact of cancer genetic information on the client's quality of life, educational and career goals, reproductive options, and other life choices. Psychosocial issues in cancer genetic counseling can be identified and addressed by integrating the principles and practices of genetic counseling, psychology, and psycho-oncology into the evaluation (Baker *et al.*, 1998).

Assessing Perception of Risk

A variety of information is collected to assess the client's perceived estimate of personal cancer risk and the methods by which decisions are made. Such information may include but is not limited to the following:

1. Motivations for seeking a cancer risk consultation. Clarify the client's goals for the consultation by determining what information she/he hopes to gain and guide the session based on those goals.
2. Beliefs about cancer etiology and perception of risk. Recognizing and addressing client beliefs about cancer etiology and risk is a critical component of educating and assisting the client in his/her adaptation to new cancer risk information.
3. Ethnocultural information. Awareness of the cultural background, religion, and ethnicity of the client can provide deeper understanding of how the individual may perceive and utilize the information (H. T. Lynch *et al.*, 1996; Mitchell, 1998).
4. Socioeconomic and demographic information. Knowing the client's age, education, occupation, and so forth, assists in targeting the appropriate degree of genetics information provided and helps to set the tone of the counseling session.
5. Psychosocial factors. Identify emotional reactions to cancer risk, such as feelings of anger, fear, and guilt, that may provide clues as to how the client and/or his/her family will cope with genetic information. Be aware that clients with increased levels of distress might not comprehend or cope with information as well as less-distressed clients (Lerman *et al.*, 1995; Audrain *et al.*, 1998). Consider referral for additional mental health

services when the client is having significant difficulty adjusting to personal circumstances or in the presence of symptoms related to a psychiatric condition. Examples might include prolonged or unresolved grief, unrealistic expectations, affective disorder, and cancer obsession, among others. Suggest that the client bring a support person (spouse, relative, friend) to their cancer genetic risk assessment sessions.

6. Cancer screening. Collect information about the client's current screening practices and ascertain whether there are potential compliance issues.
7. Health behaviors. Identify the client's perceptions about available preventive or risk-reducing therapies such as prophylactic surgery or chemoprevention. Prior to genetic testing, determine if the client anticipates that cancer genetic information will alter his/her health behaviors or decision to take part in risk-reduction strategies. Identify barriers to recommended health behaviors and explore methods to promote compliance.
8. Coping strategies. Assess the client's coping mechanisms, support systems, and cancer experiences.

Process of Psychosocial Assessment

The format of cancer genetic counseling is interactive and allows time for information gathering and dissemination. This is best achieved in a face-to-face consultation to permit assessment of both the client's verbal and nonverbal cues. A comprehensive consultation may take place over several sessions. Genetic counselors often use Carl Rogers' client-centered approach in eliciting information from patients (Rogers, 1951). Professionals performing cancer risk counseling require proficient skills in communication, critical thinking, counseling, and psychosocial assessment. In addition, they adhere to professional codes of ethics and values (Benkendorf *et al.*, 1992; Fine *et al.*, 1996; National Society of Genetic Counselors Code of Ethics, 1992).

Questionnaires and standard psychological measures can provide helpful information about demographics, family history, screening practices, and the client's psychological status. These may be sent to clients prior to their consultation, filled out at the time of the appointment, or, when relevant, completed over time (i.e., to monitor screening practices and/or psychological distress). Written or telephone correspondence are also ways of gathering psychological and other information.

Cancer Risk Assessment

The Concept of Risk

Absolute risk, which is defined as the probability that an event will occur (e.g., developing a disease) over a defined period of time, is the most beneficial way to present cancer risk information in cancer genetic counseling. Age-specific *lifetime*

risk estimates are often most applicable for medical decision making. For example, a woman may have a cumulative 30% lifetime risk of breast cancer, but only have a 5% chance of developing the disease in the next 5 years. For this reason, *interval risks*, which are lifetime risks divided into defined age intervals, may be helpful for communicating immediate versus long-range risks. Such distinctions may have bearing on screening and other cancer risk management decisions that may depend on which decade of life cancer risks are most salient. Most epidemiological studies provide relative risks versus absolute risks. *Relative risks* compare the incidence of disease in people who have a certain risk factor, like family history, to those who do not have the risk factor (control group). An *odds ratio* is an approximation of relative risk derived from case-control studies. To generate an absolute risk from a relative risk or odds ratio, it is necessary to know the expected incidence of the disease in question in the population. For instance, if the incidence of cancer X in the general population without risk factor A were 1 in 1,000, a relative risk of 2.0 would mean an absolute risk of 2 in 1,000 (0.2%) in those with risk factor A. Because the specific incidence due to a particular risk factor is often not known, relative risks/odd ratios are often of limited value in counseling patients (O'Neill, 2001).

Conveying Risk Information

During genetic counseling, clients may be presented with several risk estimates including the risk for developing specific types of cancer and the likelihood that they have a genetic mutation associated with cancer risk. Personal experience may significantly affect the way a client interprets a numerical risk. Presenting risk information in multiple ways such as a percentage and fraction is helpful. As risk data often differs between studies, presenting information as ranges is often useful. It is also important to discuss the chance of never developing the cancer in question. It may be useful to establish a context for the risk estimate by pointing out how their heritable cancer risk compares to cancer risks in the general population (Croyle and Lerman, 1999). In addition, assessment of the potential impact of the risk estimate on the client's health behavior is indicated.

Assessment of the client's perception of risk and beliefs about cancer etiology is done before presenting numerical risk information. Once the information is presented, verbal and nonverbal cues are used to assess the patient's understanding and acceptance.

Determining Cancer Risk

In cancer risk assessment, there are two aspects of risk. One is the absolute risk that the client will develop a specific type of cancer or cancers based on the family history. The second is the risk that the client carries a heritable or

germline mutation in a cancer susceptibility gene. Obtaining the genetic pedigree with medical record confirmation of cancer diagnoses is an obligatory step in accomplishing both aspects of risk assessment. Once the pedigree is procured, the next step is to attempt to classify the history as hereditary, familial, or sporadic.

1. *Hereditary cancer*. Several excellent resources review the clinical features of various hereditary cancer syndromes to help the clinician identify at-risk families (Eng *et al.*, 2001; Greene, 1997, 1999; Lindor and Greene, 1998; Maher and Hodgson, 1999; Offit, 1998; Vogelstein and Kinzler, 1997). Accurate syndrome identification is necessary to determine what types of tumors may occur in relatives, the magnitude of risk, and what gene is most likely to be involved. Even in the absence of an identifiable syndrome, any pedigree that demonstrates autosomal dominant transmission of a specific type(s) of cancer is suggestive of an inherited cancer predisposition. In families with known syndromes or dominant inheritance, first-degree relatives of affected individuals have a 50% risk of inheriting the putative cancer-predisposing gene mutation segregating in the family. Those who do not inherit the familial mutation are typically at the general population risk of cancer. Those who inherit the mutation are at increased risk of developing the associated cancers and for passing the causative gene to offspring. Most hereditary cancer syndromes are characterized by incomplete penetrance and variable expressivity. Therefore, identification of a heritable cancer susceptibility mutation generally indicates a probability that cancer will develop but not a certainty (incomplete penetrance). Furthermore, age of onset, number of primary tumors, and tumor site can vary within and among families (variable expressivity).
   a. Determining absolute cancer risk in hereditary syndromes. Cancer risk information is available for many of the defined cancer syndromes, such as hereditary breast ovarian cancer syndrome and hereditary nonpolyposis colorectal cancer syndrome. Using pedigree assessment to determine the likelihood that a client has inherited a mutation in a particular cancer-predisposing gene and data from the literature regarding cancer risk in mutation carriers, it is often possible to estimate a client's heritable cancer risk. It is critical to utilize current risk estimates from peer-reviewed research as these numbers have changed as understanding of the conditions has increased. If there is an identifiable mutation in the family, molecular testing can determine definitively whether a person inherited the familial mutation and can refine cancer risk estimation. In families with autosomal dominant transmission of a specific type of cancer without molecular evidence of an identifiable syndrome, cancer risk estimation is provided through pedigree assessment and the use of available empiric risk models (described below).

In families with known cancer syndromes, Bayes' theorem can be used to refine risk estimates as long as age-specific expression information is available for the syndrome in question. For example, relatives who have lived beyond the age at which they would likely have developed cancer if they had a mutation have a lower chance of actually carrying the mutation than is predicted by their position in the pedigree. Offit provides an in-depth review of how Bayes' theorem can be applied in cancer genetic risk assessment (Offit, 1998).

b. Determining the probability of identifying a mutation in hereditary cancer families. Models for determining the probability that genetic testing will reveal a mutation in a predisposition gene are currently available for the *BRCA1*, *BRCA2*, *MLH1*, and *MSH2* genes (Table IV). These models utilize factors such as age of onset of cancer, number of affected relatives, and presence/absence of associated malignancies in estimating the likelihood of a mutation in an affected member of the family. Ancestry may also affect the likelihood of a mutation in a family, as is the case for *BRCA1/2* mutations in Ashkenazi individuals. Once these models have been utilized in a family, pedigree analysis can then determine the likelihood that an unaffected relative will have an identifiable mutation. Knowing the probability that genetic testing will reveal a mutation is helpful for those considering molecular analysis, as many clients will have overestimated their risk (Burke, 2000). It is an important component of informed decision-making.

2. *Familial cancer*. Histories classified as familial are those in which there are more cases of a specific type(s) of cancer than expected on the basis of chance alone, but not necessarily exhibiting the classic features of hereditary cancers (early age of onset, multifocal tumors, dominant inheritance). These histories may be the result of small family size, paucity of individuals of the higher risk gender, multifactorial influences, chance clustering of sporadic cases, underreporting of cancer history in a hereditary cancer family, a cancer syndrome with reduced penetrance, or a chance limited transmission of a cancer susceptibility gene. Genetic testing is often less likely to provide additional information about cancer risk in these cases than in hereditary ones.

   a. Determining absolute cancer risk in familial cases. Statistical models are available for estimating cancer risk in familial cases of breast cancer and, to a more limited extent, colon, ovarian, and prostate cancer (Table V). These models take into account factors such as age of onset, number of affected relatives, and the degree of relationship between the patient and the affected relatives in estimating lifetime cancer risks. One model, the Gail model (Gail *et al.*, 1989), takes into account specific environmental risk factors but incorporates only limited family history information. The risks generated from such models are empiric, that is,

Table IV. Models That Estimate Risk of Carrying a Mutation in a Cancer Predisposition Gene

Model	Gene(s)	Population studied	Limitations
BRCAPro (Berry *et al.*, 1997; Euhus, 2001; Parmigiani *et al.*, 1998); http://astor.som.jhmi.edu/brcapro/	*BRCA1* and *BRCA2*	Modeled probabilities based on family history of breast and ovarian cancer in first- and second-degree relatives and cancer rates in *BRCA1/2* mutation carriers as derived from other studies. Uses Bayesian analysis to incorporate the significance of patient's age and number and age of unaffected relatives into risk calculation	Assumes that *BRCA1* and *BRCA2* are the only breast cancer predisposition genes, so may provide overestimate of likelihood of *BRCA1/2* mutation in families with breast cancer only (some of which may have a mutation in a different gene)
Couch (Couch *et al.*, 1997)	*BRCA1*	Probability of detecting a mutation on the basis of average age of onset of cancer in a family, the occurrence of ovarian cancer, and the occurrence of breast and ovarian cancer in a single individual. Probabilities for Ashkenazi and non-Ashkenazi families provided	Study based on families with an average of four affected relatives, may not be applicable to all families with a smaller number of affected individuals. Does not provide information about *BRCA2*
Frank (Frank *et al.*, 2002)	*BRCA1* and *BRCA2*	Provides estimates of mutation frequency for women with breast cancer diagnosed <50 or ovarian cancer at any age and at least a single first-degree relative with breast cancer <50 or ovarian cancer at any age	May overestimate risk for women who have only a single affected relative versus those with more extensive family histories
Myriad Genetic Laboratories Mutation Prevalence Tables; www.myriad.com	*BRCA1* and *BRCA2*	Provides estimation of mutation prevalence in Ashkenazi and non-Ashkenazi individuals. Considers cancer diagnosis, age of onset of cancer, and occurrence of breast and/or ovarian cancer in first- and second-degree relatives	Assumes 100% detection. Data is based on a highly selected population. Relies on family history information provided on test requisition form that may be incomplete or unconfirmed
Shattuck-Eidens (Shattuck-Eidens *et al.*, 1997)	*BRCA1*	Evaluates risk of mutation using logistic regression, provided in graphical form. Examines the following variables: patient disease status – unilateral versus bilateral breast cancer, with or without ovarian cancer; patient's age at diagnosis; Ashkenazi versus non-Ashkenazi ancestry; number of relatives with breast (but not ovarian) cancer; number of relatives with breast and ovarian cancer	Does not include information about family history of ovarian cancer (except in the context of a relative who has had both breast and ovarian cancer). Does not assess likelihood of *BRCA2*

Table IV. (*Continued*)

Model	Gene(s)	Population studied	Limitations
Struewing (Struewing *et al.*, 1997)	Ashkenazi mutations in *BRCA1* and *BRCA2* 187delAG (1) 5385insC (1) 6174delT (2)	Provides estimates of mutation frequency in Ashkenazi individuals based on diagnosis of breast or ovarian cancer before or after 50, for those with no personal or family history of cancer, and for those with no personal history of cancer but an affected first degree relative	Estimates limited to Ashkenazi individuals
Wijnen (Wijnen *et al.*, 1998)	*MLH1* and *MSH2*	Provides estimates of carrying a mutation in either gene based on the following and subdivided into families that meet clinical diagnostic (Amsterdam) criteria and those that do not. • Number of relatives with colorectal cancer (CRC) or endometrial cancer (EC). • Average age of onset of colorectal cancer in family. • Individuals with multiple primary HNPCC-related cancers. • Types of extracolonic tumors in a family	Includes only *MLH1* and *MSH2*
Aaltonen (Aaltonen *et al.*, 1998)	*MLH1* and *MSH2*	Provides criteria for testing for replication errors in patients with colorectal cancer: a family history of colorectal or endometrial cancer, diagnosis at less than 50, history of multiple colorectal or endometrial cancers. Recommends follow up sequence analysis for RER+ tumors	Includes only *MLH1* and *MSH2*
Syngal (Syngal *et al.*, 2000)	*MLH1* and *MSH2*	Supports use of Bethesda Guidelines in identifying candidates for mutation analysis	Includes only *MLH1* and *MSH2*

an estimate based on average risk in a population of people with similar risk factors. For individuals whose relatives have sporadic cancer, the empiric risk calculated by the Gail model may be an overestimate of actual cancer risk. In individuals whose relatives have hereditary cancer, the empiric risk may be an underestimate of actual risk (Burke *et al.*, 2000).

Table V. Models That Estimate Absolute Risk of Developing Specific Cancers in the Absence of a Mutation in a Known Gene

Model	Estimates Risk of	Factors incorporated	Limitations	Populations studied
Gail (Benichou *et al.* 1996; Gail *et al.*, 1989)	Breast cancer; provides interval risks	• Race • Age • Age at menarche • Age at first live birth • History of previous breast biopsy • Atypical hyperplasia? • Family history of breast cancer in first-degree relatives	• Limited family history information; does not incorporate the following: • Paternal family history • Age of onset of breast cancer • Relatives with bilateral or multifocal cancer • Relatives with ovarian cancer Underestimates risk for woman with inherited predisposition to cancer	30,000 predominantly Caucasian women participating in the Breast Cancer Detection Project
Claus (E. B. Claus *et al.*, 1991, 1994)	Breast cancer provides interval risks	• Family history of breast cancer in first- and selected second-degree relatives • Takes into account age of onset	• Does not take into account the following: • Women with more than 2 affected relatives • Relatives with bilateral of multifocal tumors • Nongenetic factors that may influence cancer risk • Family history of ovarian cancer	Developed from cancer steroid and hormone (CASH) population-based, case-control study involving 4,730 patients with breast cancer. Participants were primarily Caucasian
BRCAPro (Berry *et al.*, 1997; Parmigiani *et al.*, 1998)	Breast cancer; ovarian cancer; provides interval risks	• Estimates risk of breast and ovarian cancer on the basis of likelihood that person has a BRCA1/2 mutation given family history of breast and ovarian cancer first- and second-degree relatives • Incorporates person's age and unaffected relatives in calculating risk using Bayesian analysis	• Does not incorporate more distant family history • Risk estimates based on probability of BRCA1 or 2 mutation; does not take into account possibility of other breast cancer predisposition genes that may have different associated cancer risks	Modeled probabilities using Bayesian analysis and data from studies regarding cancer risks in BRCA1/2 mutation carriers

Table V. (*Continued*)

Model	Estimates Risk of	Factors incorporated	Limitations	Populations studied
Houlston (Houlston, *et al.*, 1990)	Colon cancer	• Provides estimates of risk using limited family history information (one affected first-degree relative >45, one affected first-degree relative <45, one affected second-degree relative, or two affected first-degree relatives with dominant pedigree	• Limited family history information incorporated • Based on general population colorectal cancer rates in London, which are 27% lower than rates in the United States	Patients seen at a family cancer clinic for relatives of individuals who had developed colon cancer prior to age 45. Total of 715 individuals evaluated over a 4-year period
Carter (Carter *et al.*, 1992)	Prostate cancer	• Provides an estimate of cumulative risk of prostate cancer in first-degree relatives of affected men, on the basis of the proband's age of diagnosis	• No additional family history information incorporated. Thus, may underestimate risk in relatives of probands with hereditary prostate cancer and overestimate risk in relatives of probands with sporadic disease	Families were ascertained from 740 consecutively ascertained probands undergoing radical prostatectomy at Johns Hopkins University (highly selected). Primarily Caucasian families
Gronberg (Gronberg *et al.*, 1999)	Prostate cancer	• Provides estimates of cumulative risk of prostate cancer in sons of men with prostate cancer alone, and in son of men with prostate cancer from families in which there are at least 2 cases of prostate cancer, based on age at diagnosis of the father	• Homogenous population with questionable applicability to other populations • Used only patients with a clinical diagnosis of prostate cancer • No information on second- or third-degree relatives • No inclusion of X-linked or possible recessive families	Population based cohort study including 5,706 sons of men with prostate cancer ascertained between 1959 and 1963

Empiric risks such as those cited in the Claus data set (Table V; E. Claus *et al.*, 1993; E. B. Claus *et al.*, 1991, 1994) are useful because they can demonstrate to clients that not everyone with a family history of cancer is at significantly increased risk of developing the disease. In addition, this information can be useful to clinicians in deciding how often to perform cancer screening and what interventions to offer, if any, to reduce cancer risk.

b. Determining the probability of identifying a mutation in familial cancer families. The models mentioned previously (Table IV) can be used to determine the likelihood of a heritable mutation in presumed familial histories. Reviewing these probabilities with clients provides them with statistical evidence as to why testing for mutations in hereditary cancer genes may have a low likelihood of further characterizing their cancer risk.

3. *Sporadic cancer*. Sporadic histories are those in which the cancer(s) in the family is mainly due to nonhereditary causes. When available, empiric risk data will further support this assessment. The likelihood that molecular testing will reveal a mutation in families such as these generally approaches the frequency in the general population. The exception lies with some rare tumors. For instance, up to 10% of patients with "sporadic" medullary thyroid cancers may have germline mutations in the *RET* proto-oncogene, which causes multiple endocrine neoplasia type II (Eng *et al.*, 1995; Kitamura *et al.*, 1997; Simpson *et al.*, 1990; Wiench *et al.*, 2001). In addition, up to one third of cerebellar hemangioblastomas are associated with the hereditary cancer syndrome, von Hippel–Lindau (Couch *et al.*, 2000; Richard *et al.*, 1994). Consequently, be aware of the rare tumors that have a significant a priori likelihood of being hereditary before ruling out the possibility of increased risk to other relatives (Table II).
4. *Histories of uncertain significance*. Many families presenting for cancer risk assessment have some of the features of an inherited syndrome, such as early age of onset, but without clear evidence of single gene inheritance. Several factors can lead to difficulty in pedigree assessment, including small family size, reduced penetrance (lower cancer rates than usual in mutation carriers), a paucity of susceptible gender for sex-influenced or sex-limited cancers like prostate or breast cancer, prophylactic surgeries in at-risk members, and lack of information/inaccurate information regarding key relatives in the pedigree, as can be the case with adoption. When available, providing empiric estimates of cancer risk and mutation probabilities can be useful in such families. Encourage families with histories of uncertain significance to report any new cancer diagnoses so that the pedigree can be reassessed in the future.

Given the potential complexity of pedigree interpretation, some centers have established multidisciplinary case review conferences, where pedigrees can be discussed and assessed for clues about possible inherited susceptibility. The multidisciplinary format can also facilitate discussion of the appropriate cancer risk management strategies.

Molecular Testing for Hereditary Cancer Syndromes

Consider offering molecular testing for hereditary cancer susceptibility only when a client has a significant personal and/or family history of cancer as previously described, the test can be adequately interpreted, the results will affect medical management, the clinician can provide or make available adequate genetic education and counseling, and the client can provide informed consent (ASCO, 1996). With regard to *BRCA* gene testing specifically, an updated ASCO statement recommends evaluation by a health care professional experienced in cancer genetics to determine the appropriateness of genetic testing. A previous recommendation to offer genetic testing only if the client has a greater than 10% prior probability of carrying a mutation has been deleted (ASCO, 2003). ACMG Foundation (1999), in their document "Genetic Susceptibility to Breast and Ovarian Cancer: Assessment, Counseling, and Testing Guidelines" does not establish a numerical cutoff for when cancer genetic testing should or should not be offered. However, the guideline states that testing is not recommended in situations where there is a low probability of carrying a mutation, given the financial cost of cancer genetic testing as well as the potential psychological ramifications. Furthermore, the ACMG states that to offer genetic testing is to take the responsibility, either personally or through referral to appropriate professionals, for adequate pretest education, the process of informed consent, and posttest counseling .(ACMG Foundation, 1999).

Regulation of Genetic Testing

1. *Clinical testing*. Molecular analysis is available on a clinical, fee-for-service basis, for an increasing number of genes implicated in hereditary cancer syndromes. The Clinical Laboratory Improvement Act (CLIA) establishes standards for these clinical testing laboratories. Medicare and many third-party insurance carriers require CLIA certification for reimbursement of molecular analysis. For this reason, as well as for quality control, clinical genetic tests should be ordered from CLIA-approved laboratories.
2. *Research testing*. Molecular analysis may be available within the context of a research study. Such studies must have an institutional-review-board-approved protocol and a written informed consent form that research participants are required to sign.

When both clinical and research testing is available to a client, the pros and cons of each approach should be discussed in detail. Unlike clinical laboratories, research laboratories do not have to be CLIA-approved. Therefore, the research laboratory may not be able to release results to the client unless a CLIA-approved laboratory confirms them. The turnaround time for results, if and when they are released, is generally longer for research versus clinical tests. However, a potential benefit of research testing is that tests are performed at reduced or no cost.

Pretest Genetic Counseling and Informed Consent

Prior to beginning an in-depth discussion of the benefits, risks, and limitations of genetic testing, inquire about the client's motivations and expectations for pursuing cancer genetic testing (Jacobsen *et al.*, 1997; Lerman *et al.*, 1994, 1995, 1996b; H. Lynch *et al.*, 1997; Schneider *et al.*, 1995; Struewing *et al.*, 1995).

Informed consent is a necessary component of molecular testing for hereditary cancer syndromes whether in a clinical or research setting. The process of informed consent includes a thorough discussion of the possible outcomes of testing, a review of the possible benefits, risks, and limitations, and a discussion of alternatives to molecular testing. Basic elements of informed consent in cancer genetic risk assessment and genetic counseling have been reviewed in the medical literature (ASCO, 1996; Geller *et al.*, 1997) and are described below. In general, genetic cancer susceptibility testing is not performed on persons under the age of 18 as minors may not be able to give informed consent .(MacDonald and Lessick, 2000). The exception includes cases where medical intervention is warranted in childhood such as with familial adenomatous polyposis (*APC* testing) and multiple endocrine neoplasia type II (*RET* testing; "ASHG/ACMG," 1995; Laxova, 1999).

Elements of Informed Consent for Cancer Genetic Testing.

1. *Purpose of the test and who to test*. Explain why the test is being offered, if and how the results might alter the client's cancer risk, and how the results might affect medical management. For clients who are seeking presymptomatic genetic testing, in the absence of a known mutation in their family, discuss the importance of testing an affected relative first. This approach helps determine whether there is an identifiable mutation in the gene(s) in question for which unaffected relatives can be tested. The best relative with whom to initiate genetic testing is generally one who had an early age of onset of the cancer in question and/or multifocal cancer. In some cases, an affected relative may not be available (deceased or out of contact with the family), willing, or financially able to proceed with testing. In such situations, discuss the limitations of presymptomatic testing without an identified mutation in detail with the client (see below).

2. *General information about the gene(s)*. Review cancer risks associated with gene mutations including the concepts of penetrance and variable expressivity and the possibility of genetic heterogeneity.
3. *Possible test results*. Explain the implications of all possible test results and the likelihood that the test will be informative.
   a. *Positive result: A functionally significant mutation that indicates an increased cancer risk*. The likelihood of developing various cancers depends upon the gene in which the mutation is detected and sometimes where in the gene the mutation is located. Epigenetic factors (other genes and environmental risk factors) may also modify cancer risk. In the case of presymptomatic testing, results indicate a probability of developing cancer, not a certainty, and do not indicate when cancer may develop or the tumor site.
   b. *Negative result: No mutation identified*. In the absence of a known mutation in a family, a negative result in an unaffected person with a strong family history of cancer is generally considered uninformative. The family may have a mutation in the gene tested that is not detectable with current technology. Alternatively, because many cancer syndromes are genetically heterogeneous, the family may carry a mutation in a different gene. It is important to stress the nature of an uninformative negative test result in this setting. Failure to understand the significance of an uninformative negative result may lead to failure to comply with recommended cancer screening or cancer risk reduction practices. The interpretation of the significance of a negative result in an affected person depends on the sensitivity of the genetic test, the family history, and the a priori likelihood that the individual would have had a positive result.
   c. *Negative result: Known mutation in family*. If a functionally significant mutation has been previously identified in a close biological relative and the client tests negative for the mutation, he/she is not at increased risk of developing cancer based on the family history and is instead at general population risk. Testing the client for the familial mutation only is usually sufficient. An exception may be the cases where the client belongs to an ethnic group in which common, recurrent mutations have been identified. For instance, in Ashkenazi families that carry one of the three common *BRCA1/2* mutations, relatives electing to have molecular analysis should be tested for all three mutations, not just the one identified in the family (Couch *et al.*, 1997; Frank *et al.*, 1998).
   d. *Variant of uncertain significance: An alteration in a gene has been identified but it is unknown whether the alteration will affect gene function.* Examples of variants of unknown significance can include

missense mutations of unknown functional significance or alterations in intronic sequences not known to be involved with mRNA processing. Further studies involving the client and his/her relatives as well as an improved understanding of gene function may be necessary to establish the clinical significance of a variant. Unless the variant is determined to be significant (i.e., affecting gene function), predictive genetic testing cannot be performed in other relatives. If significant family history is present, such a result does not rule out a hereditary cancer syndrome in the family, and appropriate medical management should be based on family history alone.

4. *Likelihood of positive result*. When available, use statistical models, pedigree assessment, and/or Bayes' theorem to provide the client with information about the chance that testing will reveal a mutation in the gene(s) in question. Provide clients with qualitative and/or quantitative information about the likelihood of a positive rest result (see the section Determining the probability of identifying a mutation in hereditary cancer families).
5. *Technical aspects and accuracy of the test*. Review method(s) that will be used for mutational analysis and the likelihood of a false-positive or false-negative result (sensitivity and specificity; Eng *et al.*, 2001).
6. *Economic considerations*. Apprise the client of the cost of genetic testing and that some insurance plans may not provide reimbursement for such tests. Because of the high costs of many genetic tests, it may be useful to determine insurance coverage before proceeding. Inform the client of the benefits and risks associated with pursuing reimbursement for a genetic test (see below).
7. *Risks of genetic discrimination*. Persons considering genetic testing for cancer susceptibility need to be aware of (1) the potential consequences on insurability, (2) whether the results will be disclosed to any third party (including the referring physician), and (3) whether the center initiating the testing has any confidentiality safeguards. Encourage clients to review their insurance policies prior to testing.

   Inform clients about the status and limitations of state and federal legislation providing protection against genetic discrimination in health insurance, life insurance, and employability. At the federal level, the Health Insurance Portability and Accountability Act (HIPAA) of 1996 provides some protection against genetic discrimination with regard to health insurance for individuals with group policies (http://www.hhs.gov/ocr/hipaa/) (Fleisher and Cole, 2001). Information about genetic discrimination, current legislation, and bills up for consideration can be found at the following websites: http://thomas.loc.gov, http://www.tgac.org, and http://www.nationalpartnership.org/. In addition, be familiar with the

current legislation in your state to be able to explain the protections or lack of protections it affords clients seeking genetic testing (see http://www.nhgri.nih.gov/Policy_and_public_affairs/Legislation/insure.htm).

Life and disability insurance are generally considered separately from health insurance. Some life/disability insurers now include questions regarding genetic testing on the application form. Persons who do not already have life/disability insurance at the time they are tested may jeopardize their chances of obtaining such policies if they are found to have a gene mutation.

The possibility of employment discrimination was addressed in 1995 when the Equal Employment Opportunity Commission (EEOC) issued a guideline interpreting the Americans with Disabilities Act (ADA) to prohibit workplace discrimination of healthy persons based on genetic tests (EEOC. *Compliance Manual*, Vol. 2, Section 902, Order 915.002, pp. 902–045, 1995; EEOC, 1995).

8. *Psychosocial aspects*. The components of psychosocial assessment regarding testing to be addressed include but are not limited to the following:
   a. *Anticipated reaction to results*. Discuss with the client his/her anticipated reactions to positive, negative, uninformative, or ambiguous results, and explore anticipated coping strategies (Baum *et al.*, 1997; Croyle *et al.*, 1997; Lerman *et al.*, 1997). Failure to anticipate reactions accurately can lead to increased emotional distress months after testing (Dorval *et al.*, 2000).
   b. *Timing and readiness for testing*. Ascertain the client's readiness to proceed with testing and reassure him/her that testing can be performed at a later date if preferable. Discuss the option of DNA banking when applicable.
   c. *Family issues.* Explore whether the client has discussed testing with his/her spouse or partner and family members, their reactions to obtaining genetic information, and how their reactions might influence relationships with the client. Discuss client's plans for sharing results.
   d. *Preparing for results.* Prepare the client for how results will be provided. Discuss who will be present at the session, the language used to share results, and what will happen following the results session. Refer to mental health professional if indicated.
9. *Confidentiality issues*. Prior to testing, discuss confidentiality with the client as it pertains to how or if information will be released to his/her insurer, referring physician, and other family members.
10. *Utilization of test results: Medical surveillance and preventative measures*. Review recommendations for cancer screening, available preventive measures, and the limitations of such approaches. Discuss how or if

these recommendations would change in the event of a negative versus positive genetic test result. Ascertain how the client anticipates test results will affect his/her medical management and health behaviors (Botkin *et al.*, 1996; Burke *et al.*, 1997a,b; Hartmann *et al.*, 1999, 2001; Lerman *et al.*, 1996a; H. Lynch *et al.*, 1997).

11. *Alternatives to genetic testing*. Review methods of cancer risk estimation and options for medical management in the absence of genetic testing. Not all family members will choose genetic testing as an appropriate option. Discuss the availability of DNA banking.
12. *Storage and potential reuse of genetic material*. Inform the client of the testing laboratory's policy for storage or potential reuse of genetic material.

Sample Collection

If or when a client has decided to proceed with molecular testing, coordinate sample collection and shipment. Provide the client with an estimated turnaround time for completion of genetic test results and establish a plan for disclosing results. Encourage the client to bring a support person to the results disclosure session. Inform the client that he/she has the option to withdraw from the testing process or delay results disclosure.

Results Disclosure and Posttest Counseling

This is a multi-step process, optimally done during a face-to-face meeting.

1. *Results disclosure*. After client's consent, inform him/her of the result.
2. *Significance of test results*. Review the specificity and sensitivity of the test and discuss how the client's result affects his/her cancer risk.
3. *Impact of test results*. Assess the emotional impact of the result on the client and his/her support person through verbal and nonverbal cues; provide support as needed.
4. *Medical management*. Review screening recommendations and options of cancer risk reduction, such as chemoprevention or prophylactic surgery, if available, including benefits, risks, and limitations of these options. Provide referrals to other medical professionals for additional discussions of these topics and strongly encourage compliance with screening recommendations.
5. *Informing other relatives*. Discuss cancer risks to other relatives and importance of informing family members about family history/genetic test results. Written documentation that the client can share with relatives may be provided, safeguarding confidentiality as desired by client. If a

Table VI. Selected Cancer Genetics Resources for Clients and Professionals

Client resources	■ American Cancer Society: www.cancer.org or 1-800-ACS-2345 ■ Facing Our Risk of Cancer Empowered (FORCE): www.facingourrisk.org ■ Genetic Alliance, Inc.: www.geneticalliance.org ■ Hereditary Colon Cancer Alliance: www.hereditarycc.org or 1-800-264-6783 ■ National Institutes of Cancer, Cancer information service: 1-800-4-CANCER ■ National Society of Genetic Counselors: www.nsgc.org
Professional resources	■ Online Mendelian Inheritance in Man: www.ncbi.nlm.nih.gov/Omim ■ American Society of Clinical Oncology: www.asco.org ■ BRCAPRO: www.stat.duke.edu/∼gp/brcapro.html ■ GeneTests and GeneReviews: www.genetests.org ■ *Counseling About Cancer: Strategies for Genetic Counseling* (2nd ed.), Katherine Schneider, Wiley-Liss, 2002 (ISBN 0-471-37036-3) ■ *Cancer: Principles and Practice of Oncology* (6th ed.), Vincent T. DeVita, Samuel Hellman, and Steven A. Rosenberg (Eds.), Lippincott Williams and Wilkins, 2001 (ISBN 0-781-72229-2) ■ The Concise Handbook of Family Cancer Syndrome, Noralane Lindor, Mark Greene, and the Mayo Familial Cancer Program. *J Nat Cancer Inst 90*(14), 1039–1071, 1998

high-risk client refuses to contact at-risk relatives, an ethics consult is an option (duty to warn; ASHG, 1998).

6. *Future contact*. If follow-up care will be managed elsewhere, encourage the client to maintain contact with the cancer risk assessment center for updates about their family history, the genetics of familial cancer disorders, and the management of inherited predisposition to cancer. The same applies to high-risk families with negative test results who may be candidates for future genetic tests. When available, offer clients the option of participating in long-term follow-up studies.
7. *Resources*. Provide the client with resources about cancer genetics (Table VI) and contacts with other willing clients, if desired and available. Serve as a psychosocial support resource for the client or refer to other qualified individuals if additional support is needed.

Surveillance/Treatment/Follow-Up

Follow-up for all clients seeking cancer genetic risk assessment and genetic counseling services, regardless of cancer risk category, should include a discussion of cancer screening guidelines, reviewing limitations when relevant, methods for reducing cancer risk if known, and referrals to appropriate medical professionals for long-term medical management if needed.

SUMMARY

Cancer genetic risk assessment and genetic counseling is a multistep process. The process begins by collecting information about the client's personal

medical history and family history to assess heritable cancer risk. A psychosocial assessment is also performed to determine the client's perception of risk and ability to cope with risk information. Once this information is collected, a counseling model is used to discuss risk, facilitate adjustment to risk, provide informed consent for genetic testing when applicable, and review options for medical management. Genetic counseling is an integral part of cancer genetic risk assessment that enhances clients' ability to cope with and understand the genetic information presented.

Special Cases/Exceptions to Practice Recommendations

Genetic testing of at-risk individuals during childhood: Because minors may not be able to give informed consent, in general, genetic cancer susceptibility testing is not performed on persons under the age of 18 years (MacDonald and Lessick, 2000; NSGC Position Statement, 1995, at http://www.nsgc.org). The exception includes cases where medical intervention is warranted in childhood such as with familial adenomatous polyposis (*APC* testing) and multiple endocrine neoplasia type II (*RET* testing; ASHG/ACMG, 1995; Laxova, 1999).

Adopted proband: Individuals with early-onset cancer who have no details regarding family history will be evaluated on the basis of personal medical and psychosocial history alone.

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REFERENCES

Aaltonen, L. A., Salovaara, R., Kristo, P., Canziana, F., Hemminki, A., Peltomaki, P., *et al.* (1998). Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. *N Engl J Med, 338*(21), 1481–1487.

American Cancer Society (2002). Cancer facts and figures. http://www.cancer.org.

American College of Medical Genetics Foundation (1999). *Genetic Susceptibility to Breast and Ovarian Cancer: Assessment, counseling and testing guidelines*. New York: American College of Medical Genetics Foundation.

American Society of Clinical Oncology (1996). Statement of the American Society of Clinical Oncology: Genetic testing for cancer susceptibility. *J Clin Oncol, 14*, 1730–1740.

American Society of Clinical Oncology (2003). American Society of Clinical Oncology Policy Statement Update: Genetic testing for cancer susceptibility. *J Clin Oncol, 21,* 2397–2406.

American Society of Human Genetics Social Issues Subcommittee on Familial Disclosure (1998). ASHG statement: Professional disclosure of familial genetic information. *Am J Hum Genet, 63*(3), 898–900.

Amos, C. (1994). Identifying gene–environment interactions in cancer etiology. *Cancer Bull, 46*(3), 214–219.

ASHG/ACMG Report: points to consider: Ethical, legal, and psychosocial implications of genetic testing in children and adolescents. (1995). *Am J Hum Genet, 57,* 1233–1241.

Audrain, J., Schwartz, M. D., Lerman, C., Hughes, C., Peshkin, B. N., & Biesecker, B. (1998). Psychological distress in women seeking genetic counseling for breast-ovarian cancer risk: The contributions of personality and appraisal. *Ann Behav Med, 19*(4), 370–377.

Baker, D. L., Schuette, J. L., & Uhlmann, W. R. (Eds.) (1998). *A Guide to Genetic Counseling*. New York: Wiley.

Baum, A., Friedman, A., & Zakowski, S. (1997). Stress and genetic testing for disease risk. *Health Psychol, 16*(1), 8–19.

Benichou, J., Gail, M. H., & Mulvihill, J. J. (1996). Graphs to estimate an individualized risk of breast cancer. *J Clin Oncol, 14*(1), 103–110.

Benkendorf, J., Callanan, N., Grobstein, R., Schmerler, S., & Fitzgerald, K. (1992). An explication of the National Society of Genetic Counselors (NSGC) Code of Ethics. *J Gen Counsel, 1*(1), 31–39.

Bennett, R. L. (1999). *The Practical Guide to the Genetic Family History*. New York: Wiley-Liss.

Bennett, R. L., Steinhaus, K. A., Uhrich, S. B., O'sullivan, C. K., Resta, R. G., Lochner-Doyle, D., *et al.* (1995). Recommendations for standardized human pedigree nomenclature. Pedigree Standardization Task Force of the National Society of Genetic Counselors. *Am J Hum Genet, 56*(3), 745–752.

Berry, D. A., Parmigiani, G., Sanchez, J., Schildkraut, J., & Winer, E. (1997). Probability of carrying a mutation of breast-ovarian cancer gene BRCA1 based on family history. *J Natl Cancer Inst, 89*(3), 227–238.

Biesecker, B. B. (1997). Psychological issues in cancer genetics. *Semin Oncol Nurs, 13*(2), 129–134.

Botkin, J. R., Croyle, R. T., Smith, K. R., Baty, B. J., Lerman, C., Goldgar, D. E., *et al.* (1996). A model protocol for evaluating the behavioral and psychosocial effects of BRCA1 testing. *J Natl Cancer Inst, 88*(13), 872–882.

Burke, W., Culver, J. O., Bowen, D., Lowry, D., Durfy, S., McTiernan, A., *et al.* (2000). Genetic counseling for women with an intermediate family history of breast cancer. *Am J Med Genet, 90*(5), 361–368.

Burke, W., Daly, M., Garber, J., Botkin, J., Kahn, M. J., Lynch, P., *et al.* (1997a). Recommendations for follow-up care of individuals with an inherited predisposition to cancer: II. BRCA1 and BRCA2. Cancer Genetics Studies Consortium. *JAMA, 277*(12), 997–1003.

Burke, W., Petersen, G., Lynch, P., Botkin, J., Daly, M., Garber, J., *et al.* (1997b). Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. Cancer Genetics Studies Consortium. *JAMA, 277*(11), 915–919.

Carpten, J., Nupponen, N., Isaacs, S., Sood, R., Robbins, C., Xu, J., *et al.* (2002). Germline mutations in the ribonuclease L gene in families showing linkage with HPC1. *Nat Genet, 30*(2), 181–184.

Carter, B., Beaty, T., Steinberg, G., Childs, B., & Walsh, P. (1992). Mendelian inheritance of familial prostate cancer. *Proc Nat Acad Sci USA, 89*(8), 3367–3371.

Chen, P. L., Sellers, T. A., Rich, S. S., Potter, J. D., & Folsom, A. R. (1994). Examination of the effect of nongenetic risk factors on the familial risk of breast cancer among relatives of postmenopausal breast cancer patients. *Cancer Epidemiol Biomarkers Prev, 3*(7), 549–555.

Claus, E. B., Risch, N., & Thompson, W. D. (1991). Genetic analysis of breast cancer in the cancer and steroid hormone study. *Am J Hum Genet, 48*(2), 232–242.

Claus, E., Risch, N., & Thompson, W. D. (1993). The calculation of breast cancer risk for women with a first degree family history of ovarian cancer. *Breast Cancer Res Treat, 28,* 115–120.

Claus, E. B., Risch, N., & Thompson, W. D. (1994). Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer, 73*(3), 643–651.

Couch, F. J., DeShano, M. L., Blackwood, M. A., Calzone, K., Stopfer, J., Campeau, L., *et al.* (1997). BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. *N Engl J Med*, *336*(20), 1409–1415.

Couch, V., Lindor, N. M., Karnes, P. S., & Michels, V. V. (2000). von Hippel–Lindau disease. *Mayo Clin Proc*, *75*(3), 265–272.

Croyle, R. T. (1997). Psychosocial aspects of cancer genetic testing. A research clinicians update. *Cancer*, *80*(3, suppl), 569–575.

Croyle, R. T., & Lerman, C. (1999). Risk communication in genetic testing for cancer susceptibility. *J Natl Cancer Inst Monogr* (25), 59–66.

Croyle, R. T., Smith, K. R., Botkin, J. R., Baty, B., & Nash, J. (1997). Psychological responses to BRCA1 mutation testing: Preliminary findings. *Health Psychol*, *16*(1), 63–72.

Dorval, M., Patenaude, A. F., Schneider, K. A., Kieffer, S. A., DiGianni, L., Kalkbrenner, K. J., *et al.* (2000). Anticipated versus actual emotional reactions to disclosure of results of genetic tests for cancer susceptibility: Findings from p53 and BRCA1 testing programs. *J Clin Oncol*, *18*(10), 2135–2142.

Douglas, F. S., O'Dair, L. C., Robinson, M., Evans, D. G., & Lynch, S. A. (1999). The accuracy of diagnoses as reported in families with cancer: A retrospective study. *J Med Genet*, *36*(4), 309–312.

Drovdlic, C. M., Myers, E. N., Peters, J., Baysal, B. E., Brachman, D. E., Slattery, W. H., *et al.* (2001). Proportion of heritable paraganglioma cases and associated clinical characteristics. *The Laryngoscope*, *111*, 1822–1827.

Eng, C. (2000). Will the real Cowden syndrome please stand up: Revised diagnostic criteria. *J Med Genet*, *37*, 828–830.

Eng, C. (2001). To be or not to BMP. *Nat Genet*, *28*, 105–107.

Eng, C., Brody, L. C., Wagner, T. M., Devilee, P., Vijg, J., Szabo, C., *et al.* (2001). Interpreting epidemiological research: Blinded comparison of methods used to estimate the prevalence of inherited mutations in BRCA1. *J Med Genet*, *38*, 824–833.

Eng, C., Hampel, H., & de la Chapelle, A. (2001). Genetic testing for cancer predisposition. *Annu Rev Med*, *52*, 371–400.

Eng, C., Mulligan, L. M., Smith, D. P., Healey, C. S., Frilling, A., Raue, F., *et al.* (1995). Low frequency of germline mutations in the RET proto-oncogene in patients with apparently sporadic medullary thyroid carcinoma. *Clin Endocrinol*, *43*(1), 123–127.

Equal Employment Opportunity Commission (1995). *Compliance Manual* (Vol. 2). (No. Section 902, Order 915.002).

Euhus, D. (2001). Understanding mathematical models for breast cancer risk assessment and counseling. *Breast J*, *7*(4), 224–232.

Fearon, E. R., & Vogelstein, B. (1990). A genetic model for colorectal tumorigenesis. *Cell*, *61*(5), 759–767.

Fine, B., Baker, D. L., Fiddler, M., & consortium, A. C. D. (1996). Practice-based competencies for accreditation of and training in graduate programs in genetic counseling. *J Genet Counsel*, *5*(3), 113–122.

Fleisher, L. D., & Cole, L. J. (2001). Health insurance portability and accountability act is here: What price privacy? *Genet Med*, *3*(4), 286–289.

Frank, T. S., Deffenbaugh, A. M., Reid, J. E., Hulick, M., Ward, B. E., *et al.* (2002). Clinical characteristics of individuals with germline mutations in *BRCA1* and *BRCA2*: Analysis of 10,000 individuals. *J Clin Oncol*, *20*(6), 1480–1490.

Frank, T. S., Manley, S. A., Olopade, O. I., Cummings, S., Garber, J. E., Bernhardt, B., *et al.* (2002). Sequence analysis of BRCA1 and BRCA2: Correlation of mutations with family and ovarian cancer risk. *J Clin Oncol*, *16*(7), 2417–2425.

Gail, M. H., Brinton, L. A., Byar, D. P., Corle, D. K., Green, S. B., Schairer, C., *et al.* (1989). Projecting individualized probabilities of developing breast cancer for White females who are being examined annually. *J Natl Cancer Inst*, *81*(24), 1879–1886.

Geller, G., Botkin, J. R., Green, M. J., Press, N., Biesecker, B. B., Wilfond, B., *et al.* (1997). Genetic testing for susceptibility to adult-onset cancer. The process and content of informed consent. *JAMA*, *277*(18), 1467–1474.

Greene, M. H. (1997). Genetics of breast cancer. *Mayo Clin Proc*, *72*(1), 54–65.

Greene, M. H. (1999). The genetics of hereditary melanoma and nevi. 1998 update. *Cancer*, *86*(11, Suppl), 2464–2477.

Gronberg, H., Wiklund, F., & Damber, J. E. (1999). Age specific risks of familial prostate carcinoma: A basis for screening recommendations in high risk populations. *Cancer*, *86*(3), 477–483.

Hartmann, L., Schaid, D., Woods, J., Crotty, T., Myers, J., Arnold, P., *et al.* (1999). Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. *N Engl J Med*, *340*(2), 77–84.

Hartmann, L., Sellers, T. A., Schaid, D., Frank, T. S., Soderberg, C., Sitta, D., *et al.* (2001). Efficacy of bilateral prophylactic mastectomy in BRCA1 and BRCA2 gene mutation carriers. *J Natl Cancer Inst*, *93*(21), 1633–1637.

Holtzman, N. A., Watson, M. S. (eds.) (1997). *Promoting Safe and Effective Genetic Testing in the United States: final Report of the Task Force on Genetic Testing.* National Institutes of Health/Department of Energy Working Group on Ethical, Legal and Social Implications of Human Genome Research.

Hopwood, P. (1997). Psychological issues in cancer genetics: Current research and future priorities. *Patient Educ Counsel*, *32*(1/2), 19–31.

Houlston, R. S., Murday, V., Harocopos, C., Williams, C. B., & Slack, J. (1990). Screening and genetic counselling for relatives of patients with colorectal cancer in a family cancer clinic. *BMJ*, *301*(6748), 366–368.

Howe, J. R., Bair, J. L., Sayed, M. G., Andersen, M. R., Mitros, F. A., Peterson, G. M., *et al.* (2001). Germline mutations of the gene encoding bone morphogenetic protein receptor 1A in juvenile polyposis. *Nat Genet*, *28*, 184–187.

Howe, J. R., Roth, S., Ringold, J. C., Summers, R., Jarvinen, H., Sistonen, P., *et al.* (1998). Mutations in the SMAD4/DPC4 gene in juvenile polyposis. *Science*, *280*, 1086–1088.

Jacobsen, P. B., Valdimarsdottier, H. B., Brown, K. L., & Offit, K. (1997). Decision-making about genetic testing among women at familial risk for breast cancer. *Psychosomat Med*, *59*(5), 459–466.

Kitamura, Y., Goodfellow, P. J., Shimizu, K., Nagahama, M., Ito, K., Kitagawa, W., *et al.* (1997). Novel germline RET proto-oncogene mutations associated with medullary thyroid carcinoma (MTC): Mutation analysis in Japanese patients with MTC. *Oncogene*, *14*(25), 3103–3106.

Laxova, R. (1999). Testing for cancer susceptibility genes in children. *Adv Pediatr*, *46*, 1–40.

Lerman, C., Biesecker, B., Benkendorf, J. L., Kerner, J., Gomez-Caminero, A., Hughes, C., *et al.* (1997). Controlled trial of pretest education approaches to enhance informed decision-making for BRCA1 gene testing. *J Natl Cancer Inst*, *89*(2), 148–157.

Lerman, C., & Croyle, R. T. (1996). Emotional and behavioral responses to genetic testing for susceptibility to cancer. *Oncology (Huntington)*, *10*(2), 191–195, 199; Discussion, 200–192.

Lerman, C., Daly, M., Masny, A., & Balshem, A. (1994). Attitudes about genetic testing for breast-ovarian cancer susceptibility. *J Clin Oncol*, *12*(4), 843–850.

Lerman, C., Lustbader, E., Rimer, B., Daly, M., Miller, S., Sands, C., *et al.* (1995). Effects of individualized breast cancer risk counseling: A randomized trial. *J Natl Cancer Inst*, *87*(4), 286–292.

Lerman, C., Narod, S., Schulman, K., Hughes, C., Gomez-Caminero, A., Bonney, G., *et al.* (1996a). BRCA1 testing in families with hereditary breast-ovarian cancer. A prospective study of patient decision making and outcomes. *JAMA*, *275*(24), 1885–1892.

Lerman, C., Schwartz, M. D., Lin, T. H., Hughes, C., Narod, S., & Lynch, H. T. (1997). The influence of psychological distress on use of genetic testing for cancer risk. *J Consult Clin Psychol*, *65*(3), 414–420.

Lerman, C., Schwartz, M. D., Miller, S. M., Daly, M., Sands, C., & Rimer, B. K. (1996b). A randomized trial of breast cancer risk counseling: Interacting effects of counseling, educational level, and coping style. *Health Psychol*, *15*(2), 75–83.

Lindor, N. M., & Greene, M. H. (1998). The concise handbook of family cancer syndromes. Mayo Familial Cancer Program. *J Natl Cancer Inst*, *90*(14), 1039–1071.

Love, R. R., Evans, A. M., & Josten, D. M. (1985). The accuracy of patient reports of a family history of cancer. *J Chronic Dis*, *38*(4), 289–293.

Lynch, H., Fusaro, R., Lemon, S. J., Smyrk, T., & Lynch, J. (1997). Survey of cancer genetics: Genetic testing implications. *Cancer*, *80*(Suppl), 523–532.

Lynch, H. T., Drouhard, T., Vasen, H. F., Cavalieri, J., Lynch, J., Nord, S., *et al.* (1996). Genetic counseling in a Navajo hereditary nonpolyposis colorectal cancer kindred. *Cancer*, *77*(1), 30–35.

MacDonald, D., & Lessick, M. (2000). Hereditary cancers in children and ethical and psychosocial implications. *J Pediatr Nurs*, *15*(4), 217–225.

Maher, E. R., & Hodgson, S. V. (Eds.) (1999). *A Practical Guide to Human Cancer Genetics* (2nd ed.). London: Cambridge University Press.

Marymee, K., Dolan, C. R., Pagon, R. A., Bennet, R. L., Coe, S., & Fisher, N. L. (1998). Development of critical elements of genetic evaluation and genetic counseling for genetic professionals and perinatologists in Washington State. *J Genet Counsel*, *7*, 133–165.

Mitchell, J. L. (1998). Cross-cultural issues in the disclosure of cancer. *Cancer Pract*, *6*(3), 153–160.

National Action Plan on Breast Cancer (NAPBC, 1998). *Hereditary Susceptibility to Breast and Ovarian Cancer: An Outline of Fundamental Knowledge Needed by All Health Care Professionals.* U.S. Department of Health and Human Services, Public Health Service, Office of Women's Health.

National Society of Genetic Counselors (1992). Code of Ethics *J Genet Counsel*, *1*(1), 41–43.

Neumann, H. P., Bausch, B., McWhinney, S. R., Bender, B. U., Gimm, O., Franke, G., *et al.* (2002). Germ-line mutations in nonsyndromic pheochromocytoma (See comments). *N Engl J Med*, *346*(19), 1459–1466.

Offit, K. (1998). *Clinical Cancer Genetics: Risk Counseling and Management*. New York: Wiley-Liss.

O'Neill, S. (2001). Quantitative breast cancer risk assessment. In V. G. Vogel (Ed.), *Management of Patients at High Risk for Breast Cancer* (pp. 63–93). Malden, MA: Blackwell Science, Inc.

Parmigiani, G., Berry, D., & Aguilar, O. (1998). Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. *Am J Hum Genet*, *62*(1), 145–158.

Peters, J. A., & Stopfer, J. E. (1996). Role of the genetic counselor in familial cancer. *Oncology (Huntington)*, *10*(2), 159–166, 175; Discussion, 176–156, 178.

Richard, S., Beigelman, C., Gerber, S., Van Effenterre, R., Gaudric, A., Sahel, M., *et al.* (1994). [Does hemangioblastoma exist outside von Hippel–Lindau disease?]. *Neuro-Chirurgie*, *40*(3), 145–154.

Rogers, C. R. (1951). *Client-Centered Therapy*. Boston: Houghton-Mifflin.

Schneider, K., & Garber, J. (2001). *Counseling About Cancer: Strategies for Genetic Counselors*, 2nd ed., New York: Wiley.

Schneider, K. A., Patenaude, A. F., & Garber, J. E. (1995). Testing for cancer genes: Decisions, decisions. *Nat Med*, *1*(4), 302–303.

Shattuck-Eidens, D., Oliphant, A., McClure, M., McBride, C., Gupte, J., Rubano, T., *et al.* (1997). BRCA1 sequence analysis in women at high risk for susceptibility mutations. Risk factor analysis and implications for genetic testing. *JAMA*, *278*(15), 1242–1250.

Simpson, W. J., Carruthers, J. S., & Malkin, D. (1990). Results of a screening program for C-cell disease (medullary thyroid cancer and C-cell hyperplasia). *Cancer*, *65*(7), 1570–1576.

Struewing, J. P., Hartge, P., Wacholder, S., Baker, S. M., Berlin, M., McAdams, M., *et al.* (1997). The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. *N Engl J Med*, *336*(20), 1401–1408.

Struewing, J. P., Lerman, C., Kase, R. G., Giambarresi, T. R., & Tucker, M. A. (1995). Anticipated uptake and impact of genetic testing in hereditary breast and ovarian cancer families. *Cancer Epidemiol, Biomarkers Prev*, *4*(2), 169–173.

Sweet, K. M., Bradley, T. L., & Westman, J. A. (2002). Identification and referral of families at high risk for cancer susceptibility. *J Clin Oncol*, *20*(2), 528–537.

Syngal, S., Fox, E. A., Eng, C., Kolodner, R. D., & Garber, J. (2000). Sensitivity and specificity of clinical criteria for hereditary non-polyposis colorectal cancer associated mutations in MSH2 and MLH1. *J Med Gen*, *37*, 641–645.

Tavtigian, S. V., Simard, J., Teng, D. H., Abtin, V., Baumgard, M., Beck, A., *et al.* (2001). A candidate prostate cancer susceptibility gene at chromosome 17 p [See comments]. *Nat Genet*, *27*(2), 172–180.

Theis, B., Boyd, N., Lockwood, G., & Tritchler, D. (1994). Accuracy of family cancer history in breast cancer patients. *Eur J Cancer Prev*, *3*(4), 321–327.

U.S. Preventative Serivecs Task Force, chairman Harold, C. Sox, Jr. (1995). *Guide to clinical Preventative Services.* 2nd ed., appendix A. U.S. Government Printing Office. Stock no. 017001005258.

Vogelstein, B., & Kinzler, K. W. (1993). The multistep nature of cancer. *Trends Genet*, *9*(4), 138–141.

Vogelstein, B., & Kinzler, K. W. (Eds.) (1997). *The Genetic Basis of Human Cancer*. New York: McGraw-Hill.

Wiench, M., Wygoda, Z., Gubala, E., Wloch, J., Lisowska, K., Krassowski, J., *et al.* (2001). Estimation of risk of inherited medullary thyroid carcinoma in apparent sporadic patients. *J Clin Oncol*, *19*(5), 1374–1380.

Wijnen, J. T., Vasen, H. F., Khan, P. M., Zwinderman, A. H., van der Klift, H., Mulder, A., *et al.* (1998). Clinical findings with implications for genetic testing in families with clustering of colorectal cancer. *N Engl J Med*, *339*(8), 511–518.

Willett, W. (1993). Recent findings regarding lifestyle risk factors in the epidemiology of breast and colon cancer. In R. J. Fortner (Ed.), *Accomplishments in Cancer Research* (pp. 164–178). Philadelphia: Lippincott.

Xu, J., Zheng, L., Komiya, A., Mychaleckyj, J. C., Isaacs, S. D., Hu, J. J., *et al.* (2002). Germline mutations and sequence variants of the macrophage scavenger receptor 1 gene are associated with prostate cancer risk. *Nat Genet*, *32*(2):321–325.

Zhou, X. P., Woodford-Richens, K., Lehtonen, R., Kurose, K., Aldred, M., Hampel, H., *et al.* (2001). Germline mutations in BMPR1A/ALK3 cause a subset of cases of juvenile polyposis syndrome and of Cowden and Bannayan–Riley–Ruvalcaba syndromes. *Am J Hum Genet*, *69*, 704–711.